

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/GB2005/000372

International filing date (day/month/year)
04.02.2005

Priority date (day/month/year)
06.02.2004

International Patent Classification (IPC) or both national classification and IPC
INV. C12N15/81 C12N15/63 C12N15/75 C12P21/02

Applicant
MEDICAL RESEARCH COUNCIL

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

80/588505

International application No.
PCT/GB2005/000372

AP20 Rec'd PCT/PTO 04 AUG 2006

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☒ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☒ in written format
☒ in computer readable form
 - c. time of filing/furnishing:
☒ contained in the international application as filed.
☐ filed together with the international application in computer readable form.
☒ furnished subsequently to this Authority for the purposes of search.
3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 1, 8 (partially) and 10-17 (completely)

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1 and 8 (partially) are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

- ☒ the claims, or said claims Nos. 1 and 8 (partially) are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 10-17
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form

- ☐ has not been furnished
- ☐ does not comply with the standard

- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2005/000372

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:
- ☐ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☒ not paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-9 and 8-40

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-6, 8, 9, 18-40
	No: Claims	7
Inventive step (IS)	Yes: Claims	
	No: Claims	1-9, 18-40
Industrial applicability (IA)	Yes: Claims	1-9, 18-40
	No: Claims	

2. Citations and explanations

see separate sheet

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)

International application No.
PCT/GB2005/000372
AP20 Rec'd PCT/PTO 04 AUG 2006

1. Reference is made to the following documents:

D1: Yeast, Vol. 19, No. 2, 2002, pages 141-149

D2: Gene, Vol. 155, No. 1, 1995, pages 1-7 *Murphy*

D3: Molecular Biology of the Cell, Vol. 9, No. 1, 1998, pages 29-46 *Lee*

SECTION III

2. Partial examination of claims 1 and 8.

Claims 1 and 8 refer to a cell defined by the chromosomal and extra-chromosomal genes it expresses, wherein said genes are defined only by a functional feature.

Thus, claims 1 and 8 encompass genes defined only by their desired function (essential function), contrary to the requirements of clarity of Article 6 PCT, because the result-to-be-achieved type of definition does not allow the scope of the claim to be ascertained.

The fact that any gene could be screened does not overcome this objection, as the skilled person would not have knowledge beforehand as to whether it would fall within the scope claimed, except for the genes MOB1, Cdc33, Cdc28 and Hsp10 disclosed in the description (see pages 4 and 5 and examples). Undue experimentation would be required to screen genes randomly.

Moreover, it should be considered that claims 1 and 8 relate to an extremely large number of possible genes. Support and disclosure in the sense of Articles 6 and 5 PCT is to be found however for only a very small proportion of the genes claimed (see pages 4 and 5 and examples).

The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of claims 1 and 8.

The search of claims 1 and 8, and of all claims relating to said claims (claims 2-6, 9, 18-21 and 23-40), was consequently restricted to those claimed genes which appear to be supported, i.e. the essential genes MOB1, Cdc33, Cdc28 and Hsp10.

Consequently, the examination of claims 1 and 8 is limited to the searched subject-matter.

SECTION IV

3. Unity of Invention (Article 34(3) PCT and Rules 13 and 68 PCT)

- 3.1. An application must relate to one invention only or to a group of inventions so linked as to form a single general inventive concept.

Unity of invention is fulfilled only when there is a technical relationship among the inventions involving one or more of the same or corresponding special technical features, wherein special technical features means the particular technical feature or features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art (**Rule 13.2. PCT**).

- 3.2. The technical relationship among the present subject-matter of **claims 1-40** is that they all relate to a vector comprising an essential gene and a heterologous gene.

However, this relation cannot be accepted to consist of a "special technical feature" as defined above, since it does not define a contribution which each of the different claimed inventions, considered as a whole, makes over the prior art.

In fact, vectors comprising an essential gene and a heterologous gene are known in the prior art.

See for example:

- Molecular Biology of the Cell, Vol. 9, No. 1, 1998 (pages 29-46), which discloses a plasmid comprising the essential gene MOB1 and the heterologous gene URA3;
- The Journal of Biological Chemistry, Vol. 278, No. 17, 2003 (pages 14591-14594), which discloses a plasmid comprising the essential gene CDC5 and the heterologous gene URA3;
- Yeast, Vol. 13, No. 7, 1997 (pages 647-653), which discloses plasmids comprising the essential gene CDC28 and the heterologous genes TRP1/URA3.

Hence, the general inventive concept of a vector comprising an essential gene and a

heterologous gene cannot be accepted to be novel over the prior art (**Article 33 (2) PCT**).

Thus, the application lacks unity of invention because it is considered that the following separate alleged inventions or group of alleged inventions are not so linked as to form a single general inventive concept.

Invention 1: **claims 1-9 (completely)** and **claims 18-40 (partially)** refer to a cell that expresses both chromosomal genes and extra-chromosomal genes, wherein (a) the expressed extra-chromosomal genes include a gene with an essential function, the expression of which is unconditionally required for survival of the cell, (b) the chromosomal genes do not provide that essential function, and (c) the extra-chromosomal genes include a heterologous gene, the expression of which is controlled by a promoter that is functional in the cell. Invention 1 further concerns a method for preparing said cell, as well as the starting and intermediate cells used in said method.

Invention 2: **claims 10-14 (completely)** and **claims 18-40 (partially)** refer to a vector comprising (a) an essential gene whose expression is unconditionally required for survival of a cell of interest, (b) a conditionally-required gene to allow selection of host cells which include the vector, and (c) a gene encoding a heterologous protein of interest operably linked to a promoter that is functional in the cell of interest. Invention 2 further concerns a method for preparing a cell by transforming it with said vector.

Invention 3: **claims 15-17 (completely)** and **claims 18-40 (partially)** refer to a vector comprising (a) an essential gene whose expression is unconditionally required for survival of a cell of interest, (b) a conditionally-lethal gene to allow selective killing of host cells which include the vector, wherein the essential gene is MOB1, Cdc33 or Hsp10. Invention 3 further concerns a method for preparing a cell by transforming it with said vector.

3.3. Thus, the application lacks unity of invention because it is considered that each of the

alleged inventions as listed above, has an individual and technically independent characteristic feature.

Said alleged inventions are not so linked as to form a single general inventive concept.

The different problems underlying the present invention can be defined as:

- 1 - the provision of an improved expression system, and
- 2 - the provision of an alternative vector comprising an essential gene and a heterologous gene.

The cell defined by invention 1 is the solution to the first problem and the vectors defined by inventions 2 and 3 are different solutions to the second problem, which problem has already been solved in the prior art.

- 3.4. In response to the invitation to restrict or pay additional fees, the Applicant has neither restricted nor paid additional fees for the two extra inventions.

Consequently, the present written opinion is established for the searched invention, i.e. the first invention of the application: **Invention 1: claims 1-9 (completely) and claims 18-40 (partially)**.

SECTION V

4. Novelty (Article 33(2) PCT)

Documents **D3** disclose a cell as defined in claim 7, wherein the conditionally-lethal gene is URA3 and the essential gene is MOB1.

Therefore, the subject-matter of **claim 7** is not novel over **D3-D5**.

5. Inventive Step (Article 33 (3) PCT)

The **closest prior art** to evaluate the inventiveness of *invention 1* of the present application is any of documents **D1 or D2**.

Both documents **D1** and **D2** disclose a strain deleted chromosomally for the essential gene and complemented for its function by a wild-type copy expressed from a plasmid

counter-selectable for two markers bracketing the gene. This double counter-selection system was used for the study of null alleles of essential genes, but it is further suggested that this system is applicable to a number of genetic studies of essential genes.

Recombinant expression of proteins in heterologous hosts is a routine procedure well known in the art.

In view of providing an improved expression system, the person skilled in the art does not require any inventive skills in order to use of the system of D1/D2 for the expression of a heterologous gene.

Therefore, the subject-matter of *invention 1* is not considered to involve an inventive step.

6. Further Observations

In case of filling amended claims, the applicant is requested to take account of the above comments.

The attention of the Applicant is drawn to the fact that the application may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed (**Article 34 (2)(b) PCT** and **Rule 70.2 © PCT**).

In order to facilitate the examination of the conformity of the amended application with the requirements of **Article 34 (2)(b) PCT**, the Applicant is requested to clearly identify the amendments carried out, irrespective of whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based.